REMARKS

Claims 1-7, 9, 11-22, 24, 26, and 28-33 were rejected and remain pending. In light of the following, Applicants respectfully request reconsideration and allowance of claims 1-7, 9, 11-22, 24, 26, and 28-33.

Rejections under 35 U.S.C. § 112, first paragraph

The Examiner rejected claims 31 and 32 under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement.

Applicant respectfully disagrees. A person having ordinary skill in the art at the time Applicants filed would have been able to obtain an attenuated measles virus containing point mutations. For example, a person having ordinary skill in the art at the time Applicants filed would have been able to use routine techniques to mutate attenuated measles virus and test the resulting mutated measles virus to confirm that it is attenuated. Thus, no undue experimentation is needed for a person having ordinary skill in the art to practice the presently claimed invention.

In light of the above, Applicants respectfully request withdrawal of the rejection of claims 31 and 32 under 35 U.S.C. § 112, first paragraph.

Rejections under 35 U.S.C. § 103(a)

The Examiner rejected claims 1-7, 9, 11-22, 24, and 28-33 under 35 U.S.C. § 103(a) as being unpatentable over Bateman *et al.* (*Cancer Research*, 60:1492-1497, 2000) in view of Weibel *et al.* (*Arch. Dis. Childhood*, 48:532-536, 1973) and further in light of the Lindarkis *et al.* abstract (Lindarkis *et al.*, *Gene Therapy*, 6, Suppl. 1:S4, Abstract 13 (1999)), the Bateman *et al.* 1999 abstract (Bateman *et al.*, *Gene Therapy*, 6, Suppl. 1:S6, Abstract 24 (1999)), the Taqi *et al.* reference (Taqi *et al.*, *Lancet*, May 16, p. 1112 (1981)), the Bluming *et al.* reference (Bluming *et al.*, *Lancet*, July 10, pp. 105-106 (1971)), and the Johnston *et al.* reference (*J. Virol.*, 73(8):6903-6915)).

The Examiner also rejected claims 1-7, 9, 11-22, 24, 26, and 28-33 under 35 U.S.C. § 103(a) as being unpatentable over Bateman *et al.* (*Cancer Research*, 60:1492-1497, 2000) in

view of Usonis *et al.* (*Ped. Inf. Dis. J.*, 18:42-48, 1999) and further in light of the Lindarkis *et al.* abstract (Lindarkis *et al.*, *Gene Therapy*, 6, Suppl. 1:S4, Abstract 13 (1999)), the Bateman *et al.* 1999 abstract (Bateman *et al.*, *Gene Therapy*, 6, Suppl. 1:S6, Abstract 24 (1999)), the Taqi *et al.* reference (Taqi *et al.*, *Lancet*, May 16, p. 1112 (1981)), the Bluming *et al.* reference (Bluming *et al.*, *Lancet*, July 10, pp. 105-106 (1971)), and the Johnston *et al.* reference (*J. Virol.*, 73(8):6903-6915)).

In addition, the Examiner rejected claims 16 and 17 under 35 U.S.C. § 103(a) as being unpatentable over Bateman *et al.* (*Cancer Research*, 60:1492-1497, 2000) in view of either Weibel *et al.* (*Arch. Dis. Childhood*, 48:532-536, 1973) or Usonis *et al.* (*Ped. Inf. Dis. J.*, 18:42-48, 1999) and further in view of either the Asada reference (*Cancer*, 34:1907-1928 (1974)) or the Sato reference (*Int. J. Oral Surg.*, 8:205-211 (1979)) and further in light of the Lindarkis *et al.* abstract (Lindarkis *et al.*, *Gene Therapy*, 6, Suppl. 1:S4, Abstract 13 (1999)), the Bateman *et al.* 1999 abstract (Bateman *et al.*, *Gene Therapy*, 6, Suppl. 1:S6, Abstract 24 (1999)), the Taqi *et al.* reference (Taqi *et al.*, *Lancet*, May 16, p. 1112 (1981)), the Bluming *et al.* reference (Bluming *et al.*, *Lancet*, July 10, pp. 105-106 (1971)), and the Johnston *et al.* reference (*J. Virol.*, 73(8):6903-6915)).

Further, the Examiner rejected claims 18 and 19 under 35 U.S.C. § 103(a) as being unpatentable over Bateman *et al.* (*Cancer Research*, 60:1492-1497, 2000) in view of either Weibel *et al.* (*Arch. Dis. Childhood*, 48:532-536, 1973) or Usonis *et al.* (*Ped. Inf. Dis. J.*, 18:42-48, 1999), further in view of the Duprex et al. reference (*J. Virol.*, 73:9568-9575, 1999), and further in light of the Lindarkis *et al.* abstract (Lindarkis *et al.*, *Gene Therapy*, 6, Suppl. 1:S4, Abstract 13 (1999)), the Bateman *et al.* 1999 abstract (Bateman *et al.*, *Gene Therapy*, 6, Suppl. 1:S6, Abstract 24 (1999)), the Taqi *et al.* reference (Taqi *et al.*, *Lancet*, May 16, p. 1112 (1981)), the Bluming *et al.* reference (Bluming *et al.*, *Lancet*, July 10, pp. 105-106 (1971)), and the Johnston *et al.* reference (*J. Virol.*, 73(8):6903-6915)).

Lastly, the Examiner rejected claim 20 under 35 U.S.C. § 103(a) as being unpatentable over either Galanis *et al.* (*Gene Therapy*, 6, Suppl. 1:S7, Abstract 28, (1999)) or Russell *et al.* (*Proc. Am. Assoc. Cancer Res.*, 41:259, Abstract 1648 (2000)) in view of either Weibel *et al.*

(*Arch. Dis. Childhood*, 48:532-536, 1973) or Usonis *et al.* (*Ped. Inf. Dis. J.*, 18:42-48 (1999)), and further in light of the Lindarkis *et al.* abstract (Lindarkis *et al.*, *Gene Therapy*, 6, Suppl. 1:S4, Abstract 13 (1999)), the Bateman *et al.* 1999 abstract (Bateman *et al.*, *Gene Therapy*, 6, Suppl. 1:S6, Abstract 24 (1999)), the Taqi *et al.* reference (Taqi *et al.*, *Lancet*, May 16, p. 1112 (1981)), the Bluming *et al.* reference (Bluming *et al.*, *Lancet*, July 10, pp. 105-106 (1971)), and the Johnston *et al.* reference (*J. Virol.*, 73(8):6903-6915)).

Applicants respectfully disagree for the reasons set forth in Applicants' Appeal Brief mailed August 19, 2003.

First, the claimed invention is very different from the prior art. The present claims recite a method for reducing the number of viable cancer cells by administering an attenuated measles virus to the mammal. The Bateman 2000 reference discloses the effects of transiently transfecting cultured cells with plasmid DNA encoding fusogenic membrane glycoproteins (FMGs) and the effects of vaccinating mice with tumor cells transfected with plasmid DNA encoding FMGs. Killing cells in a dish and treating animals with transfected tumor cells are vastly different from administering an attenuated measles virus to a mammal to reduce the number of viable cancer cells. The Bateman 2000 reference also discloses that established tumors can be eradicated by transduction with plasmid DNA encoding FMG cDNA. See, page 1496. This experiment, however, was performed using a different protocol as reported in a correction published in the same journal on September 1, 2000. See, page 4978. Instead of transfecting established tumors *in vivo* and assessing tumor growth, tumor cells were transfected and then implanted 24 hours later to assess their ability to grow tumors. In fact, according to the published correction, the heading on page 1496 was corrected to read as follows: "Tumorigenicity Can Be Abrogated by Pretransduction with Plasmid DNA Encoding FMG cDNA" and not "Established Tumors Can Be Eradicated by Transduction with Plasmid DNA Encoding FMG cDNA." A copy of this published correction is attached following the Appendix of Claims.

Second, none of the cited references, either alone or in combination, teaches or suggests using an attenuated measles virus as a convenient vector to deliver measles virus DNA, let alone

to reduce the number of viable cancer cells in a mammal. Again, the Bateman *et al.* 2000 reference is a research article that discloses the effects of transfecting tissue culture cells *in vitro* and the effects of transplanting transfected tissue culture cells into animals. It is noted that page 1496 of the Bateman 2000 reference discloses that ongoing experiments demonstrate that a lentiviral vector was capable of eradicating established tumors. This falls far short of suggesting that a person having ordinary skill in the art should use an attenuated measles virus to reduce the number of viable cancer cells in a mammal. In addition, it is unclear from the Bateman 2000 reference how such a lentiviral vector was used to eradicate an established tumor since the Bateman 2000 reference fails to disclose, for example, the genetic identity of the lentiviral vector, the manner in which the lentiviral vector was made and used, and the type of tumor eradicated.

The Weibel *et al.* reference is a 1973 publication that discloses vaccination results obtained from children vaccinated with a combined measles and mumps vaccine. The Weibel *et al.* reference has nothing to do with viral vectors, the use of viral vectors, or the use of attenuated measles virus to reduce the number of cancer cells in a mammal. In fact, at no point does the Weibel *et al.* reference disclose that an attenuated measles virus would be a convenient vector to deliver measles virus DNA. Applicants see no reason why a person having ordinary skill in the art would have looked to this vaccine art for teachings related to tumor eradication. The Linardakis *et al.* abstract discloses developing plasmid- and viral-vectors expressing FMGs under the control of inducible promoters. The Bateman *et al.* 1999 abstract discloses that the authors are constructing retroviral and adenoviral vectors for *in vivo* delivery to tumors. Clearly, developing viral vectors expressing FMGs under the control of inducible promoters and constructing retroviral and adenoviral vectors are unrelated to the use of an attenuated measles virus to reduce the number of viable cancer cells in a mammal. In addition, at no point does the Linardakis *et al.* abstract or the Bateman *et al.* 1999 abstract disclose that an attenuated measles virus would be a convenient vector to deliver measles virus DNA. The Taqi *et al.* reference is a 1981 report of the unexplained regression of Hodgkin's disease after measles infection in a 7-year-old girl. Likewise, the Bluming *et al.* reference is a 1971 report of the unexplained

regression of Burkitt's lymphoma in association with measles infection. Neither of these two reports discusses viral vectors or the use of viral vectors. In fact, at no point do these two reports disclose that an attenuated measles virus would be a convenient vector to deliver measles virus DNA. It is noted that the authors of the Taqi reference proposed "a trial of attenuated live measles vaccine as in adjuvant to chemotherapy in the treatment of Hodgkin's disease in children." It is unclear from this reference what the authors are proposing. The phrase "in adjuvant to chemotherapy" is not clear. Nevertheless, proposing a trial to study the possibility of using attenuated measles vaccine in some manner falls far short of suggesting that a person having ordinary skill in the art should carry out the claimed invention. In fact, a person having ordinary skill in the art at the time Applicants filed reading the unexplained associations and the 1981 proposed trial would not have been motivated, with the required reasonable expectation of success, to use an attenuated measles virus to reduce the number of cancer cells in a mammal. Thus, taken together, it is clear that a person having ordinary skill in the art at the time Applicants filed reading the cited references would not have been motivated to administer an attenuated measles virus to a mammal to reduce the number of viable cancer cells in that mammal.

The combination of cited references fails to provide any information indicating that an attenuated measles virus can be administered to a mammal to reduce the number of viable cancer cells in the mammal. In fact, a person having ordinary skill in that art at the time Applicants filed, reading the cited references would not have had any information regarding the ability of an attenuated measles virus (e.g., a nonpathogenic measles virus) to reduce the number of viable cancer cells in a mammal. It is noted that the unexplained associations reported in the Taqi *et al.* reference and the Bluming *et al.* reference were with respect to measles infections, not administration of an attenuated measles virus. Having a measles infection is quite different from receiving an attenuated measles virus such as a measles virus vaccine. In fact, measles infections typically cause rash, high fever, cough, runny nose, and red, watery eyes with complications including diarrhea, ear infections, pneumonia, encephalitis, seizures, and death. Administration of an attenuated measles virus such as a measles virus vaccine does not typically cause these

symptoms or complications. In fact, according to the Weibel *et al.* reference, the Moraten line measles vaccine may cause mild febrile reactions, rash, and generalized malaise in a portion of recipients. See, page 534. Since the cited references fail to provide the required reasonable expectation of success in achieving reduction in the number of viable cancer cells in a mammal by administering an attenuated measles virus, the presently claimed invention is not obvious.

Even assuming for the sake of argument that the Examiner established a proper *prima facie* case of obviousness, the presently claimed invention is nevertheless not obvious as evidenced by Applicants' surprising results supporting the claimed invention. At the time Applicants filed, a person having ordinary skilled in that art would have understood that reducing the number of viable cancer cells in a mammal is generally an unpredictable process. Thus, Applicants' findings regarding attenuated measles viruses and cancer cell viability within a mammal are important and unexpected results. Specifically, Applicants' originally filed specification discloses the surprising findings that attenuated measles virus, when administered to a mammal, prevents tumor growth (See, e.g., page 22), decreases the rate of tumor progression (See, e.g., page 23 and Figures 2B and C), and causes tumor regression (See, e.g., page 23 and Figure 2A). The unexpected nature of these findings highlights the non-obviousness of the presently claimed invention.

Additional evidence supporting the patentability of the presently claimed invention is the fact that the claimed invention satisfies a long-felt need that was recognized, persistent, and not solved by others. It is well established that the long-felt need is measured from the date the problem is identified, not the date of the most pertinent prior art references. See, e.g., MPEP § 716.04 and *Texas Instruments Inc. v. Int'l Trade Comm'n*, 988 F.2d 1165, 1179 (Fed. Cir. 1993).

Having the ability to reduce the number of cancer cells within a mammal is a need that has existed for many years. For example, the Stenbeck *et al.* reference (*ACTA Oncologica*, 34:881-891 (1995)) discloses three decades of data relating to cancer survival. Thus, it is clear that cancer kills many people and effective cancer treatments are needed. This need has persisted through the years and continued to exist at the time of Applicants' invention as

evidenced by the Cancer Statistics for 2000 published by the American Cancer Society. See, Greenlee *et al.*, *CA Cancer J. Clin.*, 50:7-33 (2000).

Applicants' presently claimed invention fulfills this long-felt need. For example, claim 1 recites a method for reducing the number of viable cancer cells in a mammal by administering attenuated measles virus to the mammal. Applicants' specification provides multiple working examples demonstrating the effective treatment of cancer. In fact, Applicants' specification discloses the successful use of attenuated measles viruses to prevent tumor growth, decrease the rate of tumor progression, and cause tumor regression. Thus, a person having ordinary skill in the art reading Applicants' specification would have understood that Applicants' invention provides an effective method for reducing the number of viable cancer cells in a mammal. This evidence supports the fact that the presently claimed invention is not obvious.

With respect to claims 18 and 19, Applicants respectfully submit the following. Claims 18 and 19 recite a method for reducing the number of viable cancer cells in a mammal using an attenuated measles virus genetically modified to express a marker polypeptide where expression of the marker polypeptide correlates with replication of the attenuated measles virus. The combination of cited references does not teach or suggest such a method. The Bateman *et al.* 1999 abstract discloses that cells expressing FMGs fuse with neighboring cells. The Bateman *et al.* 1999 abstract also discloses that the authors are constructing retroviral and adenoviral vectors for *in vivo* delivery to tumors. Clearly, planning the construction of retroviral and adenoviral vectors is unrelated to the use of an attenuated measles virus to reduce the number of viable cancer cells in a mammal. The Weibel *et al.* reference discloses vaccination results obtained from children vaccinated with a combined measles and mumps vaccine, while the Usonis et al. reference discloses vaccination results obtained from children vaccinated with a combined measles, mumps, and rubella vaccine. Neither reference discusses viral vectors, the use of viral vectors, or the use of attenuated measles virus to reduce the number of viable cancer cells in a mammal. The Duprex *et al.* reference merely discloses the use of a recombinant measles virus to monitor virus spread from cell to cell. At no point does this combination of references suggest that a person having ordinary skill in the art should use the recited attenuated measles virus to

reduce the number of viable cancer cells in a mammal. Thus, the cited references do not render claims 18 and 19 obvious.

With respect to claim 20, Applicants respectfully submit the following. Claim 20 recites a method for reducing the number of viable melanoma cells, carcinoma cells, glioma cells, or myeloma cells in a mammal using an attenuated measles virus. The combination of cited references does not teach or suggest such a method. The Galanis *et al.* abstract discloses that glioma cell lines transfected with plasmids encoding FMGs form syncytia. The Galanis *et al.* abstract also discloses that the authors are in the process of producing adenoviruses and bicistronic retroviruses. The Russell *et al.* abstract is similar to the Galanis *et al.* abstract. In fact, the Russell *et al.* abstract discloses that glioma cell lines transfected with plasmids encoding FMGs form syncytia. The Russell *et al.* abstract also discloses that the transfected cells have suppressed tumorigenicity and that the authors are in the process of producing viral vectors. Again, being in the process of producing viral vectors such as adenoviral and retroviral vectors is unrelated to the use of an attenuated measles virus to reduce the number of viable cancer cells in a mammal. The Weibel *et al.* reference discloses vaccination results obtained from children vaccinated with a combined measles and mumps vaccine, while the Usonis et al. reference discloses vaccination results obtained from children vaccinated with a combined measles, mumps, and rubella vaccine. Neither reference discusses viral vectors, the use of viral vectors, or the use of attenuated measles virus to reduce the number of viable cancer cells in a mammal. Taken together, it is clear that at no point does this combination of references suggest that a person having ordinary skill in the art should use an attenuated measles virus to reduce the number of viable melanoma cells, carcinoma cells, glioma cells, or myeloma cells in a mammal. Thus, the cited references do not render claim 20 obvious.

In light of the above, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. § 103.

CONCLUSION

Applicants submit that claims 1-7, 9, 11-22, 24, 26, and 28-33 are in condition for allowance, which action is requested. The Examiner is invited to call the undersigned agent at the telephone number below if such will advance prosecution of this application. The Commissioner is authorized to charge any fees or credit any overpayments to Deposit Account No. 06-1050.

Respectfully submitted,

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